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(54) Title: MULTIPARTICULATE BISOPROLOL FORMULATION (57) Abstract A multiparticulate bisoprolol formulation for once-daily oral administration, each particle of which comprises a core of bisoprolol or a pharmaceutically acceptable salt thereof surrounded by a polymeric coating, the polymeric coating being effective to achieve an initial lag of bisoprolol release <i>in vivo</i> of at least 4-6 hours following administration and thereafter maintaining therapeutic concentrations of bisoprolol for the remainder of the twenty-four hour period. The formulation can be used for night-time dosing so as to minimise the likelihood of acute cardiovascular occurrences in the well-documented high risk period in the morning.		

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Description

Multiparticulate bisoprolol formulation

5 Technical Field

This invention relates to a bisoprolol multiparticulate formulation for oral administration and, in particular, to a bisoprolol formulation for chronotherapeutic delivery which can be used for night-time dosing so as
10 to minimise the likelihood of acute cardiovascular occurrences in the well-documented high risk period in the morning.

Background Art

15 Bisoprolol (1-[4-[[2-(1-methylethoxy)ethoxy]-methyl]phenoxy]-3-[1-methylethyl)amino]-2-propanol) is a β -adrenoreceptor blocking drug which was first synthesised and developed by E. Merck (U.S. Patent No. 4,258,062) and was first introduced into the German market in 1986. It is highly β -adrenoreceptor selective and is cleared in equal parts
20 unchanged by the kidneys, and by biotransformation in the liver.

Bisoprolol is indicated for therapeutic use in the following areas; the control of arterial hypertension, the management of ischaemic heart disease, the control of some forms of cardiac arrhythmias and in the adjunctive management of hyperthyroidism.

25

Following oral administration, 90% of bisoprolol is absorbed from the gastrointestinal tract. Peak plasma concentrations are achieved after three hours, (40 ng/ml after a 10 mg dose), and appear not to be affected

by concomitant food intake or fasting. The systemic bioavailability of bisoprolol is 90% and hence pre-systemic metabolism is below 10%. The mean plasma half life of 10-12 hours is long compared to other β -blockers. About 50% is excreted unchanged in the urine, the other 50% is biotransformed in the liver with subsequent elimination of pharmacologically inactive metabolites *via* the kidneys. The pharmacokinetic properties of bisoprolol are not dependent on age or dose in the range 2.5-100 mg.

Generally β -blockers are well tolerated drugs. As far as symptomatic adverse effects are concerned, bisoprolol shows a similar pattern to other β -blockers. Dizziness, headache and tiredness are the most frequent adverse effects spontaneously mentioned by patients treated with bisoprolol. Occasionally cold extremities, sleep disturbances, gastrointestinal upset, weakness of the legs, impotence and sweating have been reported. These effects disappeared in the course of the treatment or when dosage was reduced.

It has been well documented that there is a high risk period in the morning in which there is an increase in acute cardiovascular occurrences such as sudden death, myocardial infarction and acute cerebrovascular events. Bisoprolol formulations which are currently dosed in the morning, (with an elimination half life of 10-12 hours), provide therapeutic plasma concentrations over the entire day. However, in order to ensure therapeutic plasma concentrations of bisoprolol on waking, an evening-dosed formulation might be more appropriate.

The aim of the present invention was to achieve such a bisoprolol formulation suitable for night-time dosing with the attendant advantages.

Disclosure of Invention

5

The invention provides a multiparticulate bisoprolol formulation for once-daily oral administration, each particle comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof surrounded by a polymeric coating, said polymeric coating being effective to achieve an
10 initial lag of bisoprolol release *in vivo* of at least 4-6 hours following administration and thereafter maintaining therapeutic concentrations of bisoprolol for the remainder of the twenty-four hour period.

By lag in bisoprolol release herein is meant zero or minimal
15 release.

The formulation according to the invention enables one to achieve a sufficient delay in release while the patient is asleep, immediate drug release just prior to or following wakening and additionally maintenance
20 of therapeutic concentrations over the dosing interval.

Preferably, the polymeric coating is effective to prevent quantifiable bisoprolol plasma concentrations, such as concentrations of bisoprolol greater than 1 ng/ml, *in vivo* for a period of at least 3-6 hours.

25

The initial lag period can be followed by a rapid rise in bisoprolol concentration.

Preferably, the formulation according to the invention contains a pharmaceutically acceptable salt of bisoprolol such as acid addition salts produced by reacting bisoprolol with a suitable acid to produce a

5 pharmaceutically acceptable salt. Suitable salts include those of inorganic acids such as sulphuric acid, nitric acid, hydrogen halide acids, such as hydrochloric acid or hydrobromic acid, and phosphoric acid, such as orthophosphoric acid, and organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic

10 carboxylic or sulphonic acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenyl-propionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethane-

15 sulphonic acid, ethanedisulphonic acid, 2-hydroxyethanesulphonic acid, benzenesulphonic acid, *p*-tolunesulphonic acid and naphthalene-mono- and di-sulphonic acids.

A preferred salt is bisoprolol fumarate. A particularly preferred

20 salt is bisoprolol hemifumarate, also referred to as bisoprolol fumarate 2:1.

While bisoprolol is typically available in racemic form, formulations according to the invention can contain racemic bisoprolol

25 or enantiomers of bisoprolol either as enantiomeric mixtures or as a substantially purified enantiomer. Thus, as used herein, bisoprolol refers to both racemic and enantiomeric forms of bisoprolol.

Preferably, the bisoprolol active ingredient will comprise 0.5-20%, more especially to 0.5-8%, and most especially 0.5-4% of the total weight of the multiparticulates.

5

A provisional *in vitro* dissolution profile for a bisoprolol multiparticulate formulation suitable for night-time dosing was considered to be:

10

Time (hours)	% Released
0-6	< 10%
6-7	40-60%
10	65-80%
12	> 80%
14	> 90%

In practice little correlation was found between *in vitro* release and
15 *in vivo* plasma concentration required to achieve the desired therapeutic effects. Although not wishing to be bound by any theoretical explanation of the invention, the delayed release obtained *in vivo* following night-time dosing is considered to be affected by decreased gastric and possibly intestinal motility during sleep.

20

A representative *in vitro* dissolution profile for pH independent multiparticulates is an *in vitro* dissolution which when measured in a U.S. Pharmacopoeia 2 Apparatus (Paddles) in phosphate buffer at pH 6.8 at 37°C and 50 rpm substantially corresponds to the following:

5

(a) from 0% to 10% of the total bisoprolol is released after 2 hours of measurement in said apparatus;

10

(b) from 0% to 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and

(c) greater than 50% of the total bisoprolol is released after 10 hours of measurement in said apparatus.

15

A representative *in vitro* dissolution profile for pH dependent multiparticulates is an *in vitro* dissolution which when measured in a U.S. Pharmacopoeia 1 Apparatus (Baskets) at 37°C and 50 rpm in 0.01 N HCl for the first 2 hours followed by transfer to phosphate buffer at pH 6.8 for the remainder of the measuring period substantially

20

corresponds to the following:

(a) from 0% to 10% of the total bisoprolol is released after 2 hours of measurement in said apparatus;

25

(b) less than 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and

(c) greater than 20% of the total bisoprolol is released after 10 hours of measurement in said apparatus.

A sealant or barrier layer can be applied to the core prior to the
5 application of the polymeric coating.

The sealant or barrier layer does not modify the release of bisoprolol significantly. Suitable sealants or barriers are permeable or soluble agents such as hydroxypropyl methylcellulose, hydroxypropyl
10 cellulose, hydroxypropyl ethylcellulose and xanthan gum. Hydroxypropyl methylcellulose is preferred.

Other agents can be added to improve the processability of the sealant or barrier layer. Such agents include talc, colloidal silica,
15 polyvinyl alcohol, titanium dioxide, micronised silica, fumed silica, glycerol monostearate, magnesium trisilicate or magnesium stearate or a mixture thereof.

The sealant or barrier layer can be applied from solution
20 (preferably aqueous) or suspension using a fluidised bed coater (preferably Wurster coating), or in a pan coating system.

Such sealants or barrier coatings are commercially available such
as those sold under the Trade Marks OPADRY-WHITE Y-1-7000 and
25 OPADRY OY/B/28920 WHITE each of which is available from Colorcon Limited, England.

Preferably, the bisoprolol active ingredient is applied to a non-pareil seed having an average diameter in the range of 0.4-1.1 mm, more especially 0.85-1.00 mm.

5 The cores can be formed by coating the active ingredient onto inert cores (e.g. non-pareil seeds) to form instant release multi-particulates. The active ingredient can be applied with or without additional excipients onto the inert cores. The active ingredient can be sprayed from solution (preferably aqueous) or suspension using a
10 fluidised bed coater (preferably Wurster coating), or in a pan coating system. Alternatively, the active ingredient can be applied as a powder onto the inert cores using a binder to bind the active ingredient onto the cores. Cores can also be formed by extrusion of the core with suitable plasticisers as described below and any other processing aids as
15 necessary.

A wide range of polymers can be used in the polymer coating. These polymers include enteric polymer coating materials, such as cellulose acetate phthalate, cellulose acetate triacetate, hydroxy propyl
20 methylcellulose phthalate, polyvinyl acetate-phthalate, Eudragit® polyacrylic acid and poly acrylate and methacrylate coatings such as Eudragit® S or Eudragit® L, polyvinyl acetaldiethylamino acetate, hydroxypropyl methylcellulose acetate succinate, cellulose acetate trimellitate, shellac; hydrogels and gel-forming materials, such as
25 carboxyvinyl polymers, sodium alginate, sodium carmellose, calcium carmellose, sodium carboxymethyl starch, polyvinyl alcohol, hydroxyethyl cellulose, methyl cellulose, gelatin, starch and cellulose

based cross-linked polymers in general - the degree of cross-linking should be low so as to facilitate adsorption of water and expansion of the polymer matrix, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, cross-linked starch, microcrystalline cellulose, chitin, cellulose acetate cellulose propionate, cellulose acetate propionate, cellulose acetate butyrate, cellulose triacetate, aminoacryl-methacrylate copolymer (Eudragit® RS-PM, Rohm & Haas), pullulan, collagen, casein, agar, gum arabic, sodium carboxymethyl cellulose, carboxymethyl ethyl cellulose, (swellable hydrophilic polymers) poly(hydroxyalkyl methacrylate) (m. wt. ~5k - 5,000k), polyvinylpyrrolidone (m. wt. ~10k - 360k), anionic and cationic hydrogels, polyvinyl alcohol having a low acetate residual, a swellable mixture of agar and carboxymethyl cellulose, copolymers of maleic anhydride and styrene, ethylene, propylene or isobutylene, pectin (m. wt. ~30k - 300k), polysaccharides such as agar, acacia, karaya, tragacanth, algin and guar, polyacrylamides, Polyox® polyethylene oxides (m. wt. ~100k - 5,000k), AquaKeep® acrylate polymers, diesters of polyglucan, cross-linked polyvinyl alcohol and poly N-vinyl-2-pyrrolidone, sodium starch glucolate (e.g. Explotab®; Edward Mandell C. Ltd.); hydrophilic polymers such as polysaccharides, methyl cellulose, calcium carboxymethyl cellulose, hydroxypropyl-methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, nitrocellulose, carboxymethyl cellulose, cellulose ethers, poly(ethylene terphthalate), poly(vinyl isobutyl ether), polyurethane, polyethylene oxides (e.g. Polyox®, Union Carbide), methyl ethyl cellulose, ethylhydroxy ethylcellulose, cellulose acetate, ethylcellulose, cellulose butyrate, cellulose propionate, gelatin, collagen, starch, maltodextrin, pullulan,

polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol fatty acid esters, polyacrylamide, polyacrylic acid, ammonio methacrylate copolymers such as Eudragit® RL or Eudragit® RS (e.g. Eudragit®, Rohm and Haas), other acrylic acid derivatives, sorbitan
5 esters, polydimethyl siloxane, natural gums, lecithins, pectin, alginates, ammonia alginate, sodium, calcium, potassium alginates, propylene glycol alginate, agar, gums: arabic, karaya, locust bean, tragacanth, carrageenans, guar, xanthan, scleroglucan and mixtures and blends thereof.

10

However, preferably, the polymeric coating contains a major proportion of a pharmaceutically acceptable film-forming polymer which forms an insoluble film of low permeability.

15

In one embodiment, the polymeric coating contains a minor proportion of a pharmaceutically acceptable film-forming polymer which forms an insoluble film of high permeability.

20

Further, preferably, the or each polymer is a methacrylic acid co-polymer.

~~Alternatively, the or each polymer is an ammonio methacrylate co-polymer.~~

25

However, a mixture of methacrylic acid co-polymers and ammonio methacrylate co-polymers can be used.

Methacrylic acid co-polymers which include polymers sold under the Trade Marks Eudragit S and Eudragit L by Rohm & Haas are particularly suitable for use in the formulations according to the invention.

5

These polymers are gastroresistant and enterosoluble polymers. The polymer films are insoluble in pure water and diluted acids. They dissolve at higher pHs, the value of which depends on their content of carboxylic acid. Eudragit S and Eudragit L can be used as single
10 components in the polymer coating

Alternatively, the polymers Eudragit S and Eudragit L can be combined in the one coating film in any ratio. By using a combination of the polymers theoretically results in coating films which are soluble at
15 a pH between the pHs at which Eudragit L and Eudragit S are soluble.

Ammonio methacrylate co-polymers which include polymers sold under the Trade Marks Eudragit RS and Eudragit RL by Rohm & Haas are also particularly suitable for use in the formulations according to the
20 invention. These polymers are insoluble in pure water, dilute acids, buffer solutions or digestive fluids over the entire physiological pH range. The films swell in water (and digestive fluids independently of pH). In the swollen state they are then permeable to water and dissolved actives. The permeability of the films depends on the ratio of
25 ethylacrylate (EA), methyl methacrylate (MMA) and trimethylammonioethyl methacrylate chloride (TAMCl) groups in the polymer. Those polymers having EA:MMA:TAMCl ratios of 1:2:0.2

(Eudragit RL) are more permeable than those with ratios of 1:2:0.1 (Eudragit RS). Films of Eudragit RL are described as being "insoluble films of high permeability" and films of Eudragit RS are described as being "insoluble films of low permeability".

5

Suitably the ammonio methacrylate co-polymers are combined in the ratio of Eudragit RS:Eudragit RL (90:10). However, the two polymers can be combined in a range of ratios. To create the required lag period, the polymers should preferably be combined in ratios in the
10 range of 100:0 to 80:20 Eudragit RS:Eudragit RL, more especially 100:0 to 90:10 Eudragit RS:Eudragit RL, i.e., the major portion of the film coat would be the less permeable polymer Eudragit RS.

The ammonio methacrylate co-polymers can be combined with the
15 methacrylic acid co-polymers within the one film coat in order to achieve a lag. Ratios of ammonio methacrylate co-polymer (particularly Eudragit RS) to methacrylic acid co-polymer in the range of 99:1 to 20:80 can be used to create a lag in release.

20

The two types of polymers can also be combined in any ratio in separate coats on the cores as hereafter exemplified.

~~In addition to the Eudragit polymers described above,~~ a number of
~~other such polymers can be used to create a lag in release.~~ These include
25 methacrylate ester co-polymers (e.g. Eudragit NE 30D).

Further information on the Eudragit polymers is to be found in Chemistry and Application Properties of Polymethacrylate Coating Systems" from "Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms" edited by James McGinity (Marcel Dekker Inc., New York) pg 109-114).

Preferably, the polymeric coating includes one or more soluble excipients so as to increase the permeability of the coating.

Suitably, the or each soluble excipient is selected from a soluble polymer, a surfactant, an alkali metal salt, an organic acid, a sugar and a sugar alcohol.

Such soluble excipients include polyvinyl pyrrolidone, polyethylene glycol, sodium chloride, surfactants such as sodium lauryl sulphate and polysorbates, organic acids such as acetic acid, adipic acid, citric acid, fumaric acid, glutaric acid, malic acid, succinic acid, and tartaric acid and sugars such as dextrose, fructose, glucose, lactose and sucrose, and sugar alcohols such as lactitol, maltitol, mannitol, sorbitol and xylitol, xanthan gum, dextrans, poloxamers and maltodextrins,

Polyvinyl pyrrolidone, mannitol and polyethylene glycol are the preferred soluble excipients.

Preferably, the soluble excipient is used in an amount of from 1% to 10% by weight, based on the total dry weight of the polymer.

The polymeric coating can also include one or more auxiliary agents selected from a filler, a plasticiser and an anti-foaming agent.

Representative fillers include talc, fumed silica, glyceryl
5 monostearate, magnesium stearate, calcium stearate, kaolin, colloidal silica, gypsum, micronised silica and magnesium trisilicate.

Talc is the preferred filler.

The quantity of filler used is from about 2% to about 300% by
10 weight, preferably 20 to 100%, based on the total dry weight of the polymer.

The coatings can also include a material that improves the processing of the polymers. Such materials are generally referred to as
15 "plasticisers" and include, for example, adipates, azelates, benzoates, citrates, isoebucates, phthalates, sebacates, stearates and glycols.

Representative plasticisers include acetylated monoglycerides; butyl phthalyl butyl glycolate; dibutyl tartrate; diethyl phthalate;
20 dimethyl phthalate; ethyl phthalyl ethyl glycolate; glycerin; ethylene glycol, propylene glycol; triacetin citrate; triacetin; tripropinoin; diacetin; dibutyl phthalate; acetyl monoglyceride; polyethylene glycols; castor oil; triethyl citrate; polyhydric alcohols, acetate esters, glycerol triacetate, acetyl triethyl citrate, dibenzyl phthalate, dihexyl phthalate.
25 butyl octyl phthalate, diisononyl phthalate, butyl octyl phthalate, dioctyl azelate, epoxidised tallate, triisooctyl trimellitate, diethylhexyl phthalate, di-n-octyl phthalate, di-i-octyl phthalate, di-i-decyl phthalate, di-n-

undecyl phthalate, di-n-tridecyl phthalate, tri-2-ethylhexyl trimellitate, di-2-ethylhexyl adipate, di-2-ethylhexyl sebacate, di-2-ethylhexyl azelate, dibutyl sebacate, glyceryl monocaprylate and glyceryl monocaprinate.

5

Dibutyl sebacate is the preferred plasticiser.

The amount of plasticiser to be used in the coating is preferably from about 10% to 50%, most preferably about 20%, based on the weight of the dry polymer.

10

An example of an anti-foaming agent is Simethicone. The amount of anti-foaming agent to be used in the coating is preferably from 0% to 0.5% of the final formulation.

15

The amount of coating to be used in forming the multiparticulates will be determined by the desired delivery properties, including the amount of drug to be delivered, the time delay desired, and the size of the multiparticulates. The coating polymers will be coated to 10 to 100% weight gain on the cores, preferably 25-70% polymer weight gain.

20

The coating on the multiparticulates providing the delay, including all solid components of the coating such as co-polymer, filler, plasticiser and optional additives and processing aids, is from about 11% to 450% weight gain on the cores, preferably 30% to 160% weight gain. The polymer layer can be coated by any known method, including spray application. Spraying can be carried out using a fluidised bed coater (preferably Wurster coating) or in a pan coating system.

25

The coated cores are dried or cured after application of the polymer layer(s). "Curing" means that the multiparticulates are held at a controlled temperature for a time sufficient to provide stable release rates. Curing can be performed for example in an oven or in a fluid bed
5 drier. Curing can be carried out at any temperature above room temperature.

A sealant or barrier layer can be applied to the polymeric coating.

10 The sealant or barrier layer, when such is present, can be formed of any of the materials hereinabove specified for the sealant or barrier layer applied to the core.

The sealant or barrier layer may be applied to the polymeric
15 coating to prevent agglomeration of the multiparticulates.

The invention also provides an oral dosage form containing a multiparticulate bisoprolol formulation as hereinabove defined, which is in the form of caplets, capsules, particles for suspension prior to dosing,
20 sachets or tablets.

When the dosage form is in the form of tablets, the tablets are preferably selected from disintegrating tablets, fast dissolving tablets, effervescent tablets, fast melt tablets and mini-tablets.

The dosage form can be of any shape suitable for oral administration of a drug, such as spheroidal, cube-shaped oval or ellipsoidal.

5 The dosage form will suitably contain from 1-30 mg, preferably 1.25 - 10 mg, of active ingredient. The dosage forms will be prepared from the multiparticulates in a manner known *per se*, including additional excipients, where required.

10 Brief Description of Drawings

Fig. 1 is a graph of % bisoprolol released *versus* time (hours) for encapsulated multiparticulates as described in Example 12 over a 12 hour period;

15

Fig. 2 is a graph of % bisoprolol released *versus* time (hours) for encapsulated multiparticulates as described in Example 12 over a 24 hour period; and

20

Fig. 3 is a graph of bisoprolol plasma concentration (ng/ml) *versus* time (hours) for the four products described in Example 14 and a reference.

25

The invention will be further illustrated by the following Examples.

Modes for Carrying Out the Invention

Example 1

5 Preparation of layered multiparticulates containing bisoprolol fumarate
2:1

A solution of bisoprolol fumarate 2:1 was prepared as follows. To 529.2g of purified water were added 180g of bisoprolol fumarate 2:1.

10 The mixture was stirred for 10 minutes to dissolve the drug. 10.8g of talc USP (Whitaker, Clark and Daniels Inc., South Plainfield, New Jersey, USA) were added to the solution and the mixture was stirred for 20 min.

15 The suspension was sprayed onto 0.85-1.00mm non-pareil seeds (NP Pharma SA, France) in a fluid bed apparatus (GPCG-3, Glatt) using Wurster coating. The drug was layered onto the non-pareil seeds to give a 5% drug weight gain. The spray rate for drug layering was 1.5-3.6g/min/kg, the inlet temperature was 50°C and the non-pareils were maintained at 37-42°C. The drug-loaded instant-release multiparticulates were cooled in the Glatt GPCG-3 for 10 minutes. The multiparticulates were screened to remove oversized beads and fine material.

Example 2Preparation of Eudragit RS:RL (90:10) coated multiparticulates
containing bisoprolol fumarate 2:1

5

A Eudragit RS:Eudragit RL (90:10) aqueous dispersion was prepared as follows: 0.5g of Simethicone emulsion USP (OSI Specialities, Belgium) and 300g of talc USP were added with mixing to 1139.5g of purified water. The mixture was stirred for 15 minutes. 900g
10 of Eudragit RS 30D and 100g of Eudragit RL 30D (ammonio methacrylate co-polymers in the form of aqueous dispersions from Rohm Pharma, Germany) were added to the mixture and stirred for 20 minutes. 60g of dibutyl sebacate (Morflex Inc., Greensboro, North Carolina, USA) were added to the mixture and stirred for 20 minutes.
15 The aqueous dispersion was screened through a 500 μ m sieve.

The resulting combined dispersion was sprayed onto instant release multiparticulates prepared according to Example 1, using a fluid bed apparatus as used in Example 1. Spray rate was 3-10g/min/kg, and
20 the inlet temperature was 45-50°C. The instant release multiparticulates were maintained at 30-40°C and the air volume was 150-190 m³/h. A polymer coating of 40.08% polymer weight gain was coated onto the instant release multiparticulates. The coated multiparticulates were cooled in the Glatt GPCG-3 for 30 minutes post coating, then
25 dried/cured in the following manner:

Phase 1 50°C phase: 50°C for 11 h. 25 min., temperature dropped (steamer down) to a low of 40°C over 1 h. 35 min. Temperature fluctuated between 40-56°C for 30 min. Temperature remained at 50°C for a further 34 h. 30 min;

5

Phase 2: 35°C phase: Temperature dropped to 35°C over 2 h. 25 min. Temperature remained at 35°C for a further 29 h. 9 min. (Total time at 50°C – 45 h. 55 min. Total time at 35°C – 29 h. 9 min.)

10

The multiparticulates were screened to remove oversized multiparticulates and fine material.

Example 3

15

Preparation of Eudragit RS:Eudragit RL (90:10) coated multiparticulates containing bisoprolol fumarate 2:1

Bisoprolol instant release multiparticulates (prepared according to Example 1) were coated with the Eudragit RS:Eudragit RL (90:10) aqueous dispersions (prepared according to Example 2) to a higher polymer weight gain of 50.03%. The multiparticulates were cured in the following manner:

25

50°C for 8 h. 45 min., temperature dropped (steamer down) to a low of 30°C over 5 h. 55 min. Oven reset and remained at 50°C for a further 24 h. 25 min. Oven reset again (to account for loss of

hours when steamer down). Temperature fluctuated between 38 and 53°C for 1 h. 45 min. Temperature remained at 50°C for 15 h. 38 min. Temperature ramped down to 29°C over the next 5 hr 30 mins.

5 (Total time at 50°C – 48h. 48min).

The multiparticulates were screened as described in Example 2.

Example 4

10

Preparation of Eudragit L overcoated multiparticulates containing bisoprolol fumarate 2:1

Bisoprolol instant release multiparticulates (prepared according to
15 Example 1) were coated with Eudragit RS:Eudragit RL (90:10) aqueous
~~dispersion (prepared according to Example 2) to a polymer weight gain~~
of 29.93%. The multiparticulates were cured and screened as described
in Example 2.

20

A Eudragit L polymer solution was then prepared as follows:

120g of purified water, 1705g of isopropyl alcohol and 50g of dibutyl
sebacate were mixed together and stirred for 10 minutes. 125g of talc
USP was added to the mixture and stirred for 15 minutes. 2000g of
Eudragit L 12.5 (solution of methacrylate co-polymer from Rohm
25 Pharma, Germany) was added and stirred for 15 minutes.

The resulting polymer solution was sprayed onto bisoprolol multiparticulates coated to 29.93% polymer weight gain with Eudragit RS:Eudragit RL (90:10) polymer coat described above in this Example. The Eudragit L solution was coated with a fluid bed apparatus (Glatt GPCG-3) using Wurster coating. Spray rate was 6-16 g/min/kg. and the inlet temperature was 35-40°C. The multiparticulates were maintained at 30-32°C during coating and the air volume was 120-140 m³/h. A polymer coating of 20.05% Eudragit L weight gain was coated onto the Eudragit RS:Eudragit RL (90:10) coated multiparticulates. The Eudragit L coated multiparticulates were cured in the Glatt GPCG-3 for 60 minutes post coating. The multiparticulates were screened to remove oversized multiparticulates and fine material.

Example 5

15

Preparation of Eudragit S coated multiparticulates containing bisoprolol fumarate 2:1

A Eudragit S solution was prepared as follows: 300g of purified water and 4262.5g of isopropyl alcohol were stirred together for 5 minutes. 125g of dibutyl sebacate were added and the mixture stirred for 5 minutes. 312.5g of talc USP were added to the mixture and stirred for 15 minutes. 5000g of Eudragit S 12.5 (solution of methacrylate copolymer from Rohm Pharma, Germany) was added and stirred for 30 minutes.

The resulting solution was sprayed onto instant release multiparticulates prepared according to Example 1, using a fluid bed apparatus as used in Example 1. Spray rate was 3-12g/min/kg, and the inlet temperature was 38-40°C. The instant release multiparticulates were maintained at 30-35°C and the air volume was 130-160 m³/hr. A polymer coating of 35.09% polymer weight gain was coated onto the instant release multiparticulates. The coated multiparticulates were cooled in the Glatt GPCG-3 for 10 minutes post coating, then dried/cured in the following manner:

15 h. at 40°C. Cooled to 34°C over 1 h. 45 min. Remained at 34 - 35°C for 7h. 15 min.

The multiparticulates were screened to remove oversized multiparticulates and fine material.

Example 6

In vitro dissolution of multiparticulates

20 Dissolution details for the multiparticulates produced as described in Examples 2 to 5 above are shown in Table 1 below. Multiparticulates manufactured as described in Examples 2 and 3 were tested in phosphate buffer pH 6.8 in USP II apparatus with paddles at 50rpm. Multiparticulates manufactured as described in Examples 4 and 5 were tested in 0.01N HCl for 2 h. then transferred to phosphate buffer pH 6.8 for the remainder of the testing interval. Baskets were used rather than paddles for Examples 4 and 5, at 50 rpm.

Table 1

Dissolution profiles for multiparticulates manufactured as
described in Examples 2 to 5

5

Example 2		Example 3		Example 4		Example 5	
40.08%		50.03%		20.05%		35.09%	
Eudragit		Eudragit		Eudragit L		Eudragit S coated	
RS:Eudragit RL		RS:Eudragit RL		overcoated		multiparticulates	
(90:10) coated		(90:10) coated		multiparticulates			
multiparticulates		multiparticulates					
Dissolution profile							
Time (hours)	% released	Time (hours)	% released	Time (hours)	% released	Time (hours)	% released
1	1.8	1	1.9	2	0	2	0
2	3.5	2	2.6	3	8.5	3	1.5
4	27.3	4	10.0	4	29.0	4	4.7
6	58.2	6	33.9	6	67.2	6	13.0
8	76.2	8	58.5	8	84.2	8	20.6
10	86.3	10	74.7	10	91.7	10	28.0
12	91.0	12	83.9	12	96.6	12	33.4
22	99.1	22	100.3			24	51.4

In addition to the formulations described in Examples 1 to 6 above, different polymer coating combinations were coated onto instant release multiparticulates manufactured as described in Example 1 above using the GPCG-3 or the Uni-Glatt. Examples of the additional
5 formulations manufactured are described below.

Example 7

Preparation of Eudragit RS:Eudragit RL (97.5:2.5) coated
10 multiparticulates containing bisoprolol fumarate 2:1

A Eudragit RS:Eudragit RL (97.5:2.5) aqueous dispersion was prepared as follows: 0.8g of Simethicone emulsion USP (OSI Specialities, Belgium) and 480g of talc were added with mixing to
15 1823.2g of purified water. The mixture was stirred for 15 minutes. 1560g of Eudragit RS 30D and 40g of Eudragit RL 30D (ammonio methacrylate co-polymers in the form of aqueous dispersions from Rohm Pharma, Germany) were added to the mixture and stirred for 10 minutes. 96g of dibutyl sebacate (Morflex Inc., Greensboro, North
20 Carolina, USA) were added to the mixture and stirred for 15 minutes.

The resulting combined dispersion was sprayed onto instant
release multiparticulates prepared according to Example 1 (but
manufactured on the Uni-Glatt), using a fluid bed apparatus (Uni-Glatt)
25 using Wurster coating. Spray rate was 3.2-8.6g/min/kg, and the inlet
temperature was 34-46°C. The outlet air flap setting on the Uni-Glatt
was maintained at a setting of 50. A polymer coating of 20.41%

polymer weight gain was coated onto the instant release multi-particulates. The coated multiparticulates were cooled in the Uni-Glatt for 30 minutes post coating, then dried/cured in an oven at 50°C for 86 h. The multiparticulates were screened to remove oversized
5 multiparticulates and fine material.

Example 8

Preparation of Eudragit RS:Eudragit RL (95:5) coated multiparticulates 10 containing bisoprolol fumarate 2:1

A Eudragit RS:Eudragit RL (95:5) aqueous dispersion was prepared as follows: 0.6g of Simethicone emulsion USP (OSI Specialities, Belgium) and 360g of talc were added with mixing to
15 1367.4g of purified water. The mixture was stirred for 15 minutes. 1140g of Eudragit RS 30D and 60g of Eudragit RL 30D (ammonio methacrylate co-polymers in the form of aqueous dispersions from Rohm Pharma, Germany) were added to the mixture and stirred for 10 minutes. 72g of dibutyl sebacate (Morflex Inc., Greensboro, North
20 ~~Carolina, USA) were added to the mixture and stirred for 15 minutes.~~

The resulting combined dispersion was sprayed onto instant release multiparticulates prepared according to Example 1 (but manufactured on the Uni-Glatt), using a fluid bed apparatus (Uni-Glatt)
25 using Wurster coating. Spray rate was 1.4-10.7 g/min/kg, and the inlet temperature was 38-52°C. The outlet air flap setting on the Uni-Glatt was maintained at a setting of 50. A polymer coating of 20.60%

polymer weight gain was coated onto the instant release multi-particulates. The coated multiparticulates were cooled in the Uni-Glatt for 30 minutes post coating, then dried/cured in an oven at 50°C for 48 h. The multiparticulates were screened to remove oversized
5 multiparticulates and fine material.

Example 9

Preparation of Eudragit RS:PVP K-30 (95:5) coated multiparticulates 10 containing bisoprolol fumarate 2:1

A Eudragit RS:PVP K-30 (95:5) aqueous dispersion was prepared as follows: 0.6g of Simethicone emulsion USP (OSI Specialities, Belgium) and 18g of Kollidon 30 (BASF) were added with mixing to
15 1409.4g of purified water. The mixture was stirred for 10 minutes. 360g of talc USP were added to the mixture and stirred for 15 minutes. 1140g of Eudragit RS 30D (ammonio methacrylate co-polymer in the form of aqueous dispersion from Rohm Pharma, Germany) was added to the mixture and stirred for 10 minutes. 72g of dibutyl sebacate (Morflex
20 Inc., Greensboro, North Carolina, USA) were added to the mixture and stirred for 15 minutes.

The resulting combined dispersion was sprayed onto instant release multiparticulates prepared according to Example 1, using a fluid
25 bed apparatus as used in Example 1. Spray rate was 4.2-15.2 g/min/kg, and the inlet temperature was 48-54°C. The instant release multi-particulates were maintained at 37-44°C and the air volume was

147-231 m³/h. A polymer coating of 20.86% polymer weight gain was coated onto the instant release multiparticulates. The coated multiparticulates were cooled in the Glatt GPCG-3 for 30 minutes post coating, then dried/cured in an oven at 50°C for 46 h. The
5 multiparticulates were screened to remove oversized multiparticulates and fine material.

Example 10

10

In vitro dissolution of multiparticulates

Dissolution details for the multiparticulates produced as described in Examples 7 to 9 above are shown in Table 2 below. All multiparticulates manufactured as described in these Examples were tested in
15 phosphate buffer pH 6.8 in USP 2 apparatus with paddles at 50rpm.

Table 2

Dissolution profiles for multiparticulates manufactured as
described in Examples 7 to 9

5

Example 7		Example 8		Example 9	
20.41% Eudragit RS:Eudragit RL (97.5:2.5) coated multiparticulates		20.60% Eudragit RS:Eudragit RL (95:5) coated multiparticulates		20.86% Eudragit RS:PVP K-30 (95:5) coated multiparticulates	
Dissolution profile					
Time (hours)	% released	Time (hours)	% released	Time (hours)	% released
1	1.3	1	0.8	1	1.7
2	2.4	2	1.4	2	2.6
3	3.8	3	2.9	4	9.1
4	5.9	4	6.1	6	20.8
5	8.8	5	10.9	8	32.2
6	12.3	6	17.0	10	40.6
7	15.8	7	26.4	12	47.2
8.5	21.2	8.5	38.1		
10	27.4	10	48.7		

Combination of one or more types of coated multiparticulates, such as those described in Examples 2-5 and 7-9, may also be used to form suitable formulations. However, a two component system formed by mixing two populations of coated multiparticulates chosen from those
5 in Examples 2-5 and 7-9 appears to offer no particular advantage over a single component system with respect to achieving a suitable *in vitro* release.

Examples 11 and 12 are examples of bisoprolol delayed release
10 multiparticulates including a sealant or barrier layer.

Example 11

Step A: Preparation of layered multiparticulates containing
15 bisoprolol.

A solution of bisoprolol was prepared as follows. To 529.2g of purified water were added 180g of bisoprolol fumarate 2:1. The mixture was stirred for 10 minutes to dissolve the drug. 10.8g of talc USP
20 (Whitaker, Clark and Daniels Inc., South Plainfield, New Jersey, USA) were added to the solution and the mixture was stirred for 20 minutes.

The suspension was sprayed onto 0.85-1.00mm non-pareil seeds (NP Pharma SA, France) in a fluid bed apparatus (GPCG-3, Glatt) using
25 Wurster coating. The drug was layered onto the non-pareil seeds to give a 5% drug weight gain. The spray rate for drug layering was 1.5-3.6g/min/kg, the inlet temperature was 50°C and the non-pareils were

maintained at 37-42°C. The drug loaded instant release multiparticulates were cooled in the Glatt GPCG-3 for 10 minutes. The multiparticulates were screened to remove oversized beads and fine material.

5 Step B: Coating instant release multiparticulates with barrier layer.

A suspension of Opadry White in water was prepared as follows:
To 900.0g of purified water were added 100.0g of Opadry White Y-1-
10 7000 (Colorcon Ltd, England) with stirring. The mixture was stirred for a further 45 minutes to disperse the Opadry White. The suspension was screened through a 500µm screen.

The suspension was sprayed onto the instant release bisoprolol
15 multiparticulates (manufactured as described in Step A) in a fluid bed apparatus (GPCG-3, Glatt) using Wurster coating. The Opadry White was layered onto 2.2Kg of instant release multiparticulates to give 2% solids weight gain. The spray rate for coating with the Opadry White suspension was 1.7-2.5g/min/kg, the inlet temperature was 44-47°C and
20 the non-pareils were maintained at 36-39°C. The Opadry coated multiparticulates were cooled in the Glatt GPCG-3 for 10 minutes. The multiparticulates were screened to remove oversized beads and fine material.

25 Step C: Preparation of Eudragit RS:Eudragit RL (90:10) coated multiparticulates containing bisoprolol.

A Eudragit RS:Eudragit RL (90:10) aqueous dispersion was prepared as follows: 1.6g of Simethicone emulsion USP (OSI Specialities, Belgium) and 960g of talc USP were added with mixing to 3646.4g of purified water. The mixture was stirred for 15 minutes. 2880g of Eudragit RS 30D and 320g of Eudragit RL 30D (ammonio methacrylate co-polymers in the form of aqueous dispersions from Rohm Pharma, Germany) were added to the mixture and stirred for 20 minutes. 192g of dibutyl sebacate (Morflex Inc., Greensboro, North Carolina, USA) were added to the mixture and stirred for 20 minutes. The aqueous dispersion was screened through a 500µm sieve.

The resulting combined dispersion was sprayed onto the 2% Opadry White coated multiparticulates prepared according to Step B, using a fluid bed apparatus as used in Step A. Spray rate was 2.7-10.9g/min/kg, and the inlet temperature was 45-48°C. The Opadry White coated multiparticulates were maintained at 28-40°C and the air volume was 149-169 m³/hr. A polymer coating of 29.96% polymer weight gain was coated onto the Opadry White multiparticulates. The coated multiparticulates were cooled in the Glatt GPCG-3 for 30 minutes post coating.

A further 10.65% polymer weight gain was achieved by continuing the coating of the Eudragit RS:Eudragit RL (90:10) aqueous dispersion onto 1.00Kg the 29.96% polymer coated multiparticulates in the Glatt GPCG-3. Spray rate was 7.7-11.3g/min/kg, and the inlet temperature was 46-49°C. The 29.96% polymer coated multiparticulates

were maintained at 32.9-40.4°C and the air volume was 126-136 m³/hr. The total polymer coating applied to the Opadry White coated multiparticulates at the end of this process was 40.61% polymer weight gain. The coated multiparticulates were cooled in the Glatt GPCG-3 for
5 30 minutes post coating. The coated multiparticulates were dried/cured in an oven at the following temperatures and times:

Phase 1: 50°C for 33 hr 25 minutes, temperature dropped to a low of 32°C for 2 hours, temperature returned to 50°C for a further 12 h. 35 min. Temperature dropped to 35°C over 2 hours (problem
10 with oven – temperature fell below 35°C to low of 24°C - below 35°C for 17.45 hours). Returned to 35°C for further 28 hours 45 minutes.

The multiparticulates were screened to remove oversized
15 multiparticulates and fine material.

Dissolution results for 40.61% Eudragit RS:Eudragit RL (90:10) coated multiparticulates manufactured to include a barrier coat of Opadry White are shown in Table 3.

20

Dissolution method

Apparatus: USP 2 apparatus (Paddles)

Speed: ~~50-rpm~~

Medium: Phosphate buffer pH 6.8 at 37°C.

25

Table 340.61% Eudragit RS:Eudragit RL (90:10) coated multiparticulates with

5

Opadry White barrier layer

Dissolution profile	
Time (hours)	% bisoprolol released
1	2.3
2	13.4
4	61.5
6	82.4
8	92
10	96.1
12	98.6
22	102.7

Example 12

Step A: Preparation of layered multiparticulates containing bisoprolol.

5

As described under Example 11, Step B.

Step B: Coating instant release multiparticulates with barrier layer.

10

A suspension of Opadry Aqueous Moisture Barrier in water was prepared as follows: To 1350g of purified water were added 150.0g of Opadry OY/B/28920 White (Colorcon Ltd, England) with stirring. The mixture was stirred for a further 45 minutes to disperse the Opadry

15 White. The suspension was screened through a 500µm screen.

The suspension was sprayed onto the instant release bisoprolol multiparticulates (manufactured as described in Step A) in a fluid bed apparatus (GPCG-3, Glatt) using Wurster coating. The Opadry Aqueous

20 Moisture Barrier was layered onto 1.5Kg of instant release multiparticulates to give 3% solids weight gain. The spray rate for coating with the Opadry Aqueous Moisture Barrier suspension was 2.7-4.6g/min/kg, the inlet temperature was 49-55°C and the non-pareils were maintained at 39.9-44.9°C during the coating process. The Opadry
25 coated multiparticulates were dried in the Glatt GPCG-3 for 5 minutes,

then cooled for 16 minutes in the Glatt. The multiparticulates were screened to remove oversized beads and fine material.

Step C: Preparation of Eudragit RS:Eudragit RL (90:10) coated
5 multiparticulates containing bisoprolol.

A Eudragit RS:Eudragit RL (90:10) aqueous dispersion was prepared as follows: 0.9g of Simethicone emulsion USP (OSI Specialities, Belgium) and 108g of Dibutyl sebacate (Morflex Inc.,
10 Greensboro, North Carolina, USA) were added with mixing to 2051.1g of purified water. The mixture was stirred for 10 minutes. 540g of Talc USP were added to the mixture and stirred for 15 minutes. 1620g of Eudragit RS 30D and 180g of Eudragit RL 30D (ammonio methacrylate co-polymers in the form of aqueous dispersions from Rohm Pharma,
15 Germany) were added to the mixture and stirred for 15 minutes.

The resulting combined dispersion was sprayed onto the 3% Opadry Aqueous Moisture Barrier coated multiparticulates prepared according to Step B, using a fluid bed apparatus as used in Step A.

20 ~~Spray rate was 5.0-11.7 g/min/kg, and the inlet temperature was 45-~~

48°C. The Opadry Aqueous Moisture Barrier coated multiparticulates

~~were maintained at 32.8-40.9°C and the air volume was 119-158 m³/hr.~~

A polymer coating of 29.84% polymer weight gain was coated onto the

Opadry White multiparticulates. The coated multiparticulates were dried
25 post coating in the Glatt GPCG-3 for 1 hour at inlet temperature of 45-

~~55°C then cooled for 5 minutes. The multiparticulates were then dried in~~

an oven for 48 hours at 50°C. The temperature dropped to 35°C over the

next 1.5 hours, then the temperature was maintained at 35°C for the next 13.75 hours. The multiparticulates were screened to remove oversized multiparticulates and fine material.

- 5 Dissolution results for 29.84% Eudragit RS:Eudragit RL (90:10) coated multiparticulates manufactured to include a barrier coat of Opadry Aqueous Moisture Barrier are shown in Table 4:

Dissolution method

- 10 Apparatus: USP 2 apparatus (Paddles)
Speed: 50 rpm
Medium: Phosphate buffer pH 6.8 at 37°C.

Table 4

29.84% Eudragit RS:Eudragit RL (90:10) coated multiparticulates

5

Dissolution profile	
Time (hours)	% bisoprolol released
1	1.6
2	7.1
4	48.2
6	73.7
8	85.0
10	91.0
12	93.8
22	99.2

Example 13

10

Preparation of capsules containing 5mg of bisoprolol fumarate 2:1

Coated multiparticulates manufactured as described in Examples

2-5 were encapsulated in size 2 hard gelatin capsules to give dosage forms containing the equivalent of 5mg of bisoprolol fumarate 2:1. The dissolution methods used for the encapsulated multiparticulates were as follows:

15

Examples 2 and 3:

Apparatus: USP 2 apparatus (Paddles)

Speed: 50 rpm

5 Medium: Phosphate buffer pH 6.8 at 37°C

Examples 4 and 5

Apparatus: USP 1 apparatus (Baskets)

Speed: 50 rpm

10 Medium: 0.01N HCl for the first 2 hours. Then transferred to
phosphate buffer pH 6.8 for the remainder of the testing period.

Temperature 37°C

The results are shown in Figs. 1 and 2 wherein:

15

A = The product of Example 2

B = The product of Example 3

20

C = The product of Example 4

D = The product of Example 5.

25

Example 14Biostudy

5 An open label, single dose, five treatment, five period, balanced, randomised crossover study was designed to compare the bioavailability of the formulations described in Examples 2-5 and as encapsulated according to Example 13 (5 mg bisoprolol fumarate 2:1) relative to a reference Concor® 5mg tablet (E. Merck). Fifteen healthy male
10 volunteers were dosed as one group with each volunteer being dosed on five occasions with at least a seven-day washout period between each dose. The volunteers fasted from food and beverages other than water for at least four hours prior to dosing in each treatment period and water was proscribed one hour before and one hour after dosing. The
15 Volunteers were fed an evening meal (approximately 17:00 hours) and dosing occurred at night (approximately 22.00 hours) followed by at least a 10-hour fast. Venous blood specimens were obtained from the volunteers at regular time intervals following each dosing.

20 Two volunteers dropped out of the study and samples from two other volunteers were lost leaving eleven evaluable/crossed-over subjects. The mean plasma concentrations for bisoprolol for these eleven volunteers are shown in Fig. 3. Labels A, B, C and D refer to the encapsulated formulations in Example 13 and E refers to the reference
25 product. As shown in Table 5, all four formulations according to the invention achieved a lag compared to the reference product indicating

that a formulated lag is required to develop a PM administered bisoprolol product.

Table 5

5

PK Parameter	A	B	C	D	E
C _{max} (ng/ml)	12.697 ± 2.752	10.742 ± 2.076	13.704 ± 3.539	10.893 ± 3.807	19.479 ± 3.593
AUC(0-∞) (ng/ml.h)	305.931 ± 80.795	272.686 ± 58.646	317.212 ± 87.166	282.318 ± 82.646	317.796 ± 91.951
T _{max} (h)	14.909 ± 2.071	20.727 ± 4.221	13.818 ± 1.662	20.636 ± 5.259	2.591 ± 1.530
T _{quant} * (h)	4 - 6	8 - 10	2 - 3	8 - 14	

*T_{quant} reported as a range in the time prior to the first quantifiable bisoprolol plasma concentration.

10

CLAIMS: -

1. A multiparticulate bisoprolol formulation for once-daily oral administration, each particle comprising a core of bisoprolol or a
5 pharmaceutically acceptable salt thereof surrounded by a polymeric coating, said polymeric coating being effective to achieve an initial lag of bisoprolol release *in vivo* of at least 4-6 hours following administration and thereafter maintaining therapeutic concentrations of bisoprolol for the remainder of the twenty-four hour period.
- 10 2. A multiparticulate bisoprolol formulation according to Claim 1, wherein the polymeric coating is effective to prevent quantifiable bisoprolol plasma concentrations *in vivo* for a period of at least 3-6 hours.
- 15 3. A multiparticulate bisoprolol formulation according to Claim 1 or 2, which contains a pharmaceutically acceptable salt of bisoprolol.
4. A multiparticulate bisoprolol formulation according to Claim 3,
20 wherein the salt is bisoprolol hemifumarate.
5. A multiparticulate bisoprolol formulation according to any
~~preceding claim~~, which has an *in vitro* dissolution profile which when
measured in a U.S. Pharmacopoeia-2 Apparatus (Paddles) in phosphate
25 buffer at pH 6.8 at 37°C and 50 rpm substantially corresponds to the
following:

(a) from 0% to 10% of the total bisoprolol is released after 2 hours of measurement in said apparatus;

(b) from 0% to 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and

(c) greater than 50% of the total bisoprolol is released after 10 hours of measurement in said apparatus.

- 10 6. A multiparticulate bisoprolol formulation according to any preceding claim, which has an *in vitro* dissolution profile which when measured in a U.S. Pharmacopoeia 1 Apparatus (Baskets) at 37°C and 50 rpm in 0.01 N HCl for the first 2 hours followed by transfer to phosphate buffer at pH 6.8 for the remainder of the measuring period
- 15 substantially corresponds to the following:

(a) from 0% to 10% of the total bisoprolol is released after 2 hours of measurement in said apparatus;

20 (b) less than 50% of the total bisoprolol is released after 4 hours of measurement in said apparatus; and

(c) greater than 20% of the total bisoprolol is released after 10 hours of measurement in said apparatus.

7. A multiparticulate bisoprolol formulation according to any preceding claim, wherein a sealant or barrier layer is applied to the core prior to the application of the polymeric coating.
- 5 8. A multiparticulate bisoprolol formulation according to Claim 7, wherein the sealant or barrier is selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose and xanthan gum.
- 10 9. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the bisoprolol active ingredient is applied to a non-pareil seed having an average diameter in the range of 0.4-1.1mm.
- 15 10. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating contains a major proportion of a pharmaceutically acceptable film-forming polymer which forms an insoluble film of low permeability.
- 20 11. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating contains a minor proportion of a pharmaceutically acceptable film-forming polymer which forms an insoluble film of high permeability.
- 25 12. A multiparticulate bisoprolol formulation according to Claim 10 or 11, wherein the or each polymer is a methacrylic acid co-polymer.

13. A multiparticulate bisoprolol formulation according to Claim 10 or 11, wherein the or each polymer is an ammonio methacrylate co-polymer.

5 14. A multiparticulate bisoprolol formulation according to Claim 12 or 13, wherein a mixture of said polymers is used.

15. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating includes one or more
10 soluble excipients so as to increase the permeability of the coating.

16. A multiparticulate bisoprolol formulation according to Claim 15, wherein the or each soluble excipient is selected from a soluble polymer, a surfactant, an alkali metal salt, an organic acid, a sugar and a sugar
15 alcohol.

17. A multiparticulate bisoprolol formulation according to Claim 15 or 16, wherein the soluble excipient is selected from polyvinyl pyrrolidone, polyethylene glycol and mannitol.

20

18. A multiparticulate bisoprolol formulation according to any one of Claims 15-17, wherein the soluble excipient is used in an amount of from 1% to 10% by weight, based on the total dry weight of the polymer.

25 19. A multiparticulate bisoprolol formulation according to any preceding claim, wherein the polymeric coating includes one or more

auxiliary agents selected from a filler, a plasticiser and an anti-foaming agent.

20. A multiparticulate bisoprolol formulation according to any
5 preceding claim, wherein the coating polymer is coated to 10% to 100% weight gain on the core.

21. A multiparticulate bisoprolol formulation according to any
preceding claim, wherein the coating polymer is coated to 25% to 70%
10 weight gain on the core.

22. A multiparticulate bisoprolol formulation according to any
preceding claim, wherein a sealant or barrier layer is applied to the
polymeric coating.

15

23. A multiparticulate bisoprolol formulation according to Claim 22,
wherein the sealant or barrier is selected from hydroxypropyl
methylcellulose, hydroxypropyl cellulose, hydroxypropyl ethylcellulose
and xanthan gum.

20

24. An oral dosage form containing a multiparticulate bisoprolol
formulation according to any one of Claims 1-23, which is in the form of
caplets, capsules, particles for suspension prior to dosing, sachets or
tablets.

25

25. An oral dosage form according to Claim 24, which is in the form of tablets selected from disintegrating tablets, fast dissolving tablets, effervescent tablets, fast melt tablets and mini-tablets.
- 5 26. A multiparticulate bisoprolol formulation according to Claim 1, substantially as hereinbefore described and exemplified.
27. An oral dosage form according to Claim 24, substantially as hereinbefore described.

INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/IE 00/00005

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/135 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 463 877 A (TANABE SEIYAKU) 2 January 1992 (1992-01-02) claims 1,3,4 page 3, line 12 - line 17 examples 12,10	1-6, 9-14, 19-27
X	WO 98 32426 A (POLIN INDUSTRIA CHIMICA) 30 July 1998 (1998-07-30) claims 1-5 page 5, line 21 -page 6, line 11	1-6, 9-15, 17-21, 24-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

17 April 2000

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

information on patent family members

Intern Application No

PCT/IE 00/00005

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